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Vol. 115. SEPTEMBER, 1943 No. 9

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Published monthly by the Philadelphia College of Pharmacy and Science 43rd Street, Kingsessing and Woodland Avenues, Philadelphia, Pa.

Annual Subscription, $3.00 — **Foreign Postage, 25 Cents Extra**
Single Numbers, 30 Cents — **Back Numbers, 50 Cents**

Entered as Second-Class Matter at the Post Office at Philadelphia, Pa. Under Act of March 3, 1879

Acceptance for Mailing at Special Rate of Postage Provided for in Section 1103 Act of October 3, 1917. Authorized February 15, 1920

OUR COVER

DR. ROBERT P. FISCHELIS

Remington Medalist for 1943

THE Committee on Award of the Remington Honor Medal has announced that its selection for the year 1943 is Robert P. Fischelis. This annual award is bestowed "upon that man or woman who has done most for American Pharmacy during the preceding year or during a longer period of outstanding activity and of fruitful achievement."

The choice of Dr. Fischelis for this highest award in pharmacy is in our opinion most appropriate. His activities in behalf of pharmacy are impressive both by reason of their number and their character. Dr. Fischelis prior to 1926 was Dean of the New Jersey College of Pharmacy in which position he had the opportunity of intimate contact with the educational phase of pharmacy. Since that time he has been closely connected with state administrative work in pharmacy and is at present Secretary of the Board of Pharmacy of the State of New Jersey and its chief chemist. As editor of the *New Jersey Journal of Pharmacy* and as author and co-author of a number of texts he has had wide experience in journalism. Dr. Fischelis has made commendable progress in establishing pharmacy in its proper place in the public health picture and he serves as a member of the State Board of Health in New Jersey and Chairman of the Joint Committee of the A. Ph. A. and the American Social Hygiene Association.

Since December, 1941, Dr. Fischelis has devoted much of his time as head of the Chemicals, Drugs, and Health Supplies Branch of the Office of Civilian Requirements in Washington, D. C. In this important position he has demonstrated exceptional administrative abilities.

The influence that Dr. Fischelis exerts for the improvement and advancement of real pharmacy is well-known. He is a clear thinker, an indefatigable worker, and one who inspires in those with whom he works profound respect. The cause of pharmacy would be greatly strengthened and its future much brighter if more key men in its organizations were patterned like him.

E D I T O R I A L

THE PENNSYLVANIA FORMULARY

PHARMACISTS and physicians in the State of Pennsylvania recently received the first edition of the Pennsylvania Formulary. This collection of formulas was published under the auspices of a Joint Committee representing both the State Medical Society and the Pennsylvania Pharmaceutical Association.

Such collaborative effort is, in itself, praiseworthy since much is to be gained by closer cooperation between the medical and pharmaceutical professions. We have in a number of states, notably New Jersey and Florida, excellent formularies similarly promoted by joint action on the part of the medical and pharmaceutical groups.

Examination of the Pennsylvania Formulary, however, brings forth an admixture of chagrin, disgust and dismay. It is unbelievable that two presumably learned professions in the great State of Pennsylvania could put their stamp of authorization on such an illiterate hodge-podge of formulas. It is obvious that no responsible task of editing this compilation was performed else the multitude of errors in spelling and its numerous inconsistencies could not have been made.

Any schoolboy could have made dozens of corrections in the manuscript which apparently were unnoticed by the editorial staff. One could forgive the exceedingly careless use of Latin and its devious blend with English but simple everyday English is even mutilated.

A few nice examples of crude titles and spelling follow:

"immissible"
"self-mendication"
"Elixer Aminophyllini"
"Cordiale Glycerophos Comp. With B_1"
"Elixir Hypertensi No 1"
"Ingrofix"
"Pulvis Conspersus Antifungi"

The language throughout is poorly chosen and unscientific and not what one might expect from a group of scientifically trained specialists.

A further point that is questionable is the evident attempt to encourage physicians to employ drugs of obscure origin in place of legitimate proprietaries of known manufacture and control. There is no doubt but that pharmacists face real difficulties in attempting to supply the plethora of proprietaries now currently prescribed, but any effort to divert this practice by means which in themselves are an even greater evil do not appear to this writer, at least, commendable.

In searching for a possible explanation of the very low quality of the Pennsylvania Formulary only one seems likely. Surely the many men of sound judgment in both professional organizations are guilty only of misplaced confidence in the person or persons to whom this task was assigned. There are many capable men who could, and should, be asked immediately to revise this book. The reputation and honor of both professions demand that this be done without delay. Until it is we all stand embarrassed by an unfortunate act in which most of us had no part.

L. F. Tice.

FOOD POISONING

Bacterial Toxins and Infections

By Cora B. Gunther, B. S., M. S.*

THE term "food poisoning" ** is used to describe a sudden, explosive gastroenteritis following the eating of contaminated food. It is characterized by nausea, vomiting, headache, diarrhea, cramps and in some cases chills and fever and extreme prostration. It seldom proves fatal, except in Botulism, and usually lasts less than twenty-four hours or in a few cases a period of several days. The condition may be caused by chemicals, poisonous plants, some animals, also bacteria and their products. Cases due to bacteria and their products are by far the most common.

Food poisoning outbreaks due to bacteria are of two types: first, the toxic type caused by ingestion of food containing preformed bacterial toxins, and second, the infection type caused by the eating of food containing large numbers of living organisms. Botulism and staphylococcus poisoning are examples of the first type, and Salmonellae and Streptococci cause the second type. Staphylococcus food poisoning is characterized by a shorter incubation period than that found in the types due to infection.

Botulism results from the ingestion of preformed toxin produced by the growth of Cl. botulinum in underprocessed food, mostly home-canned vegetables and fruit in this country and preserved meats in Europe. Symptoms appear in one to two days. The term "Botulism" is derived from the word "botulus" meaning sausage, the first case being reported in Europe in 1735. Cl. botulinum is a gram positive, anaerobic spore-bearing organism whose natural habitat is soil. The spores are ubiquitous and may be found at any time, anywhere, making food contamination almost inevitable. They are very resistant to heat; under favorable conditions they may resist boiling for five and one-half hours. It is obvious from this fact that the cold

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**Much material used in the preparation of this paper has been taken from "Food Poisoning," by G. M. Dack. The University of Chicago Press, Chicago, Ill. (1943).

pack method of home-canning should be abandoned in favor of the pressure-cooker method. The toxin, however, is less resistant to heat and poisoning can be avoided by boiling five to fifteen minutes in an open vessel, in order to destroy the toxin, before tasting. Numerous canned and processed vegetables, fruits and meats have caused Botulism. Home-canned string beans head the list as having caused the greatest number of outbreaks.

Laboratory diagnosis is best made by testing for the toxin rather than culturing for the organism, since preformed toxin must be ingested to produce the disease. Ingestion of spores, washed free of toxin, is harmless and toxin is not formed in the intestinal tract. Since spores are ubiquitous they may be present in any food without the presence of toxin.

Material to be tested is usually suspected food, vomitus or stomach washings or portions of material obtained from the bowel at autopsy. Toxin can also be demonstrated in the blood and organs of fatal cases. This is sometimes important where samples of ingested food are not available. Some information can be gained from inspection of canned goods. Bulging of cans may or may not occur and food may or may not show any odor or gross signs of spoilage. If the food has a pH of 5.4 or lower it is not likely to contain Cl. botulinum, as growth below this pH is uncertain. A high salt content is also unfavorable for growth of the organism.

Botulinus toxin is one of the most potent toxins known. A fatal dose of toxin for an adult man may be as small as $\frac{1}{100}$ mgm. or less. There are five types, A to E. The toxins of A and B and rarely E cause human Botulism, while those from types C and D cause the disease in animals. Since it is a true exotoxin and is antigenic, each toxin type produces a specific antitoxin which can be used in testing for the presence of toxin in suspected materials. Briefly, the method consists in grinding the material to be tested with sterile sand and saline, centrifuging, and inoculating mice intraperitoneally. Control mice are protected by types A, B, and E antitoxins. The animals showing protection determine the type. Guinea pigs and other animals can also be used.

Staphylococcus food poisoning, as in Botulism, is caused by the ingestion of preformed toxin. It is the most common of all food poisonings, the first case being reported as early as 1894. The symptoms are different from those of Botulism. They appear in about

three hours, the illness being of shorter duration, and recovery usually rapid and complete.

The conditions necessary to produce staphylococcus poisoning are, first, contamination with an enterotoxin-producing strain of staphylococcus; second, a suitable food in which they can grow; third, keeping the food for a sufficient time and a temperature compatible with growth.

First, staphylococci are ubiquitous, being found on the normal skin, in pimples and boils, and are found in great numbers in the post-nasal drip following colds. They may also be present in the air. Under these conditions contamination of food is inevitable. The percentage of staphylococci which produce enterotoxin has not been definitely determined. Dolman (1) states that very likely only a small number are involved, but Wilson (2) states that roughly 40 per cent from various sources are enterotoxigenic as shown by the kitten test.

Second, many different foods appear to be suitable for growth and enterotoxin production. Custard-filled bakery products are responsible for the most outbreaks, ham and tongue next. Foods such as ham which are preserved by high salt or sugar concentration are especially favorable media for staphylococci, since they are highly resistant to salt and sugar. Salmon will support the growth of staphylococci, but enterotoxin is not formed. Dried beef, cream, cake, cheese, chicken gravy and many other foods are favorable media for enterotoxin production.

Third, enterotoxin is not formed at refrigerator temperatures, 4° to 7° C., but is formed at room temperature after five hours or less. It is stable at refrigerator temperatures and resists boiling for at least thirty minutes.

Laboratory diagnosis of staphylococcus food poisoning is not such a simple matter. Inspection of suspected food gives no information, since there is no odor or other evidence of spoilage, although it is very easy to demonstrate staphylococci in food. The food can be ground with sterile sand and saline dilutions plated in veal agar and a rough estimate of the numbers of organisms made. Blood agar, Endo and S. S. (Salmonella-Shigella) media are streaked to rule out Salmonellae and streptococci. The presence of large numbers of staphylococci in the suspected food and a short incubation period presents circumstantial evidence of staphylococcus food poisoning. Since

staphylococci are ubiquitous the contamination of "leftover" food may have taken place after part of the food was eaten, and they might also be of a non-enterotoxigenic type.

Many attempts have been made to correlate cultural, biochemical or serologic reactions of staphylococci with enterotoxin production. None of these have been successful. S. aureus is incriminated in more outbreaks than S. albus. Liquefaction of Stone's gelatin and growth on mannitol agar are of no value. There is no correlation between the production of hemolysins, dermonecrotizing and lethal toxins and the production of enterotoxin. A strain may produce other potent toxins but not enterotoxin and vice versa. Enterotoxin-producing strains may fall in any serologic group. Stritar and Jordan (3) conclude that the power to provoke food poisoning is not limited to any recognizable variety of staphylococcus.

The best that can be done by cultural or biochemical methods is to test the isolated strains for over-all pathogenicity. Eighty-five per cent of S. aureus and 10 per cent of S. albus are pathogenic. In general the pathogenic strains are highly pigmented and hemolytic. There is 98 per cent correlation between pathogenicity and coagulase production. Testing for coagulase production is a simple test and if positive indicates a pathogenic strain. This is done by inoculating plasma with a loopful of the culture and incubating three hours or longer. Clotting of the plasma is a positive test.

Detection of the enterotoxin itself by some laboratory method would be the ideal solution. Unfortunately, no entirely satisfactory test has been devised as yet. Enterotoxin is not a true exotoxin and is not antigenic in the same sense that Botulinus toxin is and cannot be detected by animal protection tests with specific antitoxin. It is a complex carbohydrate; true exotoxins are proteins. No direct chemical test has yet been devised to detect it. The only highly susceptible animal is man. The usual laboratory animals are relatively resistant to the toxin by oral administration.

The next best step is to see whether the staphylococci will produce enterotoxin under experimental conditions. The organisms are grown on special media under increased CO_2 tension and the filtrate boiled for thirty minutes to destroy other toxins. The amount of enterotoxin has to be large to affect the relatively insusceptible animal. Jordan and McBroom (4) have shown that symptoms can be produced by feeding and intravenous injection of Rhesus monkeys.

Monkeys, however, are expensive and difficult to handle and relatively insusceptible when compared to humans and in addition they become resistant after several feedings.

The Dolman (5) kitten test, which consists of the intraperitoneal and intravenous inoculation of six to eight-weeks-old kittens, appears to be the most satisfactory and economical method to date. Symptoms can be produced by both methods of inoculation, but it has been shown that intraperitoneal injection of sterile broth alone may give rise to symptoms, making it necessary to test each kitten first, with sterile broth. Adult cats have been found satisfactory for the intravenous test. The test with kittens and cats, however, must be used on a large scale in many laboratories before its merits can be assessed. Suckling pigs have recently been shown to be good test animals.

Salmonella food poisoning is a true infection, no exotoxin being involved. The incubation period is longer than in the toxin types, usually seven to seventy-two hours. Laboratory diagnosis of Salmonella infection can be conclusively made by isolation of a strain of Salmonella from the feces and the suspected food. The organisms sometimes appear in pure culture in the feces during the acute symptoms, but usually disappear rapidly after cessation of symptoms. Agglutinins have been shown to appear in the blood, but too late for help in diagnosis. The usual selective media for the isolation of enteric organisms is used. Selenite F enrichment and S. S. plating media are favorable for the isolation of the Salmonella group. By means of cultural and biochemical tests, it can be determined whether an organism falls in the Salmonella group and the type or species is determined serologically.

The Salmonella group (6) of organisms is composed of about 112 different species or types and identification of all these types presents no small bacteriological problem. It is, however, possible to determine each type exactly by means of antigenic analysis; i. e., by testing for the antigenic components of each strain. Each strain is given an antigenic formula depending on its somatic and flagellar constituents. Each strain has a different mosaic of antigens. By means of specific and absorbed sera the presence of certain antigens can be detected by slide agglutination and the findings compared with the known antigenic composition of known type strains. The 112 strains fall into six general groups A to F, depending on the presence of a common somatic antigen. Maintaining a large type culture col-

lection, preparing absorbed sera and checking require more work than can be carried out in most diagnostic laboratories. After preliminary study, strains can be sent to typing centers for type determination. Two are available: The Salmonella Typing Center, Beth Israel Hospital, New York, or the National Salmonella Typing Center, Lexington, Ky.

Salmonellae produce in man three types of clinical pictures: First, Fever; Second, Septicemia; Third, Gastroenteritis. Of the 112 different types, 97 have been isolated from man; 86 of these cause disease in man. Of the 86 causing disease, 72 have been reported as causing gastroenteritis. Of the total number of strains causing disease, roughly, one-half are from gastroenteritis cases. S. typhimurium is found most frequently (approximately one-third of all gastroenteritis strains). Next in order of frequency of isolation are: S. oranienburg, S. montevideo, S. newport, S. enteritidis and S. panama.

In general, considering their source, Salmonellae fall into two classes, those of human origin and those of animal origin. The typhoid bacillus, Para A and B, are found principally in man. They usually cause prolonged fever and are transmitted from man to man by food, etc. All the others are of animal origin; i. e., animals are the primary hosts and the vehicle of infection is food. They usually cause septicemia in animals and generally gastroenteritis in man. There are some marked exceptions. Some animal strains cause more than one type of disease and Para B, a human strain, can cause food poisoning. The animal strains are transmitted to man mostly through food animals, but never from man to man, except from adults to infants. Infants are very susceptible to strains of animal origin but not to strains of human origin. There is a direct correlation between the types found in food animals and those found in man in various countries. Infection takes place through diseased meat, infected eggs, contamination of other foods by sewage, rat excreta, fly vectors or human carriers. The carrier state in man produced by animal strains is generally not so persistent as with human strains, usually lasting a year or less. There are, however, marked exceptions to this rule. Persons excreting S. bareilly and S. worthington for over a year have been reported and S. montediveo has been isolated from the gallbladder during surgical operations. We have on record a patient who has been a carrier of S. panama for almost a year.

Regardless of the duration of the carrier condition, the Salmonella strains from food poisoning cases are excreted for varying periods of time and constitute a serious menace in food handlers. In a series of 492 Salmonellas reported by Edwards (7), one-quarter of all strains isolated were from normal people, approximately five-sixths of these cases being of animal origin. In our series of 62 strains, 4 were from normal people, 2 of these from food handlers. Since food poisoning outbreaks are usually not reportable and the quarantine laws in many states do not cover these strains, proper control over these patients cannot be exercised.

The importance of carriers of food poisoning strains among food handlers in the armed forces is brought out by a recent report by Stone (8). A systematic survey of 2000 food handlers in camps in the Panama Canal zone yielded 42 carriers of Salmonella strains representing 13 different food poisoning types. The medical history of most of these food handlers was essentially negative.

Salmonellae are widely distributed in animals. They have been found in rats, mice, hogs, cattle, sheep, horses, dogs, cats, foxes, chinchillas, rabbits, guinea pigs and fowl. Data on the distribution of types furnish valuable leads in tracing the origin of infection. Some strains causing human disease are found only in one animal host such as S. abortus equi in horses, and S. choleraesuis is found most frequently in swine. S. typhimurium is found in more different hosts and in greater numbers than any other strain; this accounts, no doubt, for its frequency in human food poisoning. More different types and in greater numbers have been isolated from fowl than from any other group of animals.

In view of these epidemiological observations it becomes apparent how important it is to type strains of Salmonellae. It is extremely important to differentiate between strains which are culturally and serologically very similar but differ widely in their distribution, as for example Para B and S. typhimurium. If a Para B strain is isolated, search for a human source would be instituted; if a S. typhimurium strain, an animal source would be sought. A mistake in definite identification can seriously hamper the epidemiological investigation.

The identification of all Salmonella strains is helpful in diagnosis and treatment of enteritides. It is especially valuable in infants, since if the early diagnosis of Salmonella enteritis is made, septicemia can

often be prevented. There is an indication that the sulfa-drugs show some differential effects on certain strains. Aside from the practical help in diagnosis and treatment of Salmonelloses, the typing of all strains from human and animal sources is of great importance in the continued study of their epidemiology and pathology.

Streptococci, alpha type, have been reported as causing food poisoning outbreaks. By means of human volunteers it has been demonstrated that the presence of the organism is necessary to produce symptoms, since filtrates from cultures are inocuous. Streptococcus food poisoning is also characterized by a long (five to eighteen hours) incubation period.

Coliform organisms and the Proteus group have also been implicated in food poisoning. There is evidence that in cases where drinking water is accidentally contaminated with sewage many outbreaks of gastroenteritis have followed with only a few cases of typhoid fever. None of these outbreaks have been investigated bacteriologically. It is entirely possible that they might have been caused by a Salmonella since they are very common in sewage. On the other hand some aberrant coliform organisms are definitely pathogenic.

Proteus is a common contaminant of food, especially meats, and its presence does not prove that it has caused the symptoms. Intraperitoneal injection of kittens with Proteus filtrates has produced symptoms. It has been shown, however, that the filtrates of cultures of gram negative rods may be toxic when injected into animals but entirely without effect when fed to man.

From a review of the literature the food poisoning role of Coliform and Proteus groups has not been established.

In summary, it has been shown that there are two types of bacterial food poisoning, the toxin and "infection" types. Botulism and staphylococcus food poisoning are of the toxin type, while Salmonella and Streptococcus poisonings are of the infection type. The former, toxin type, is characterized by a shorter incubation period (three hours) than that of the latter, infection type, (seven to seventy-two hours). Methods of laboratory diagnosis have been discussed. Botulism is the least frequent but clinical symptoms are severe and mortality high, while staphylococcus food poisoning is the most common, clinical symptoms being comparatively mild and mortality low. Salmonella food poisoning has been found to be much more frequent and caused by a larger number of strains since typing of strains has been

more widely instituted than has been generally realized. The widespread occurrence of Salmonella strains in man and animals constitutes a serious public health problem. The role of the Coliform and the Proteus groups of organisms in food poisoning has not been substantiated.

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DETERMINATION OF THE POTENCY OF DIGITALIS LEAVES GROWN IN BOGATÁ (COLOMBIA)*

By K. Mezey, M. D.**

DIGITALIS seeds were introduced into Colombia from Europe about the middle of the nineteenth century. Digitalis purpurea and Digitalis lanata now grow wild in great abundance over a large portion of the Oriental Andes at an altitude of from 1800 to 2900 meters above sea level.

In order to find the potency of the Colombian Digitalis the plant was submitted to a biological assay in cats, modifying in several points the technic described by Hatcher & Brody (1). Previous de-determinations (2) proved this method to be the most accurate. It is understood that all the details of the experiments were followed step by step.

The method developed by Straub and Houghton could not be used owing to the fact that neither Rana temporaria nor Rana pipiens exist in Colombia. Furthermore we were informed by the Committee of Revision of the Pharmacopœia of the United States that assay on cats was to be recommended for the U. S. P. XII.

The technic used in our experiments was as follows:

1. *Preparation of leaves and extracts to be examined.* Leaves of Digitalis purpurea and Digitalis lanata were collected during the months of May and November, 1942, and during the months of February and March, 1943. Only clean leaves two years old were picked, these being desiccated in an oven at a temperature of 38° C. for a period of from eighteen to twenty-four hours. The leaves were then finely triturated and after mixing the lots, the water content was determined. The powder was then stored in tightly stoppered amber jars and kept in a dry place.

To find the biological value of the powder, aqueous (infusion), alcolholic (tincture) and glycerin extracts were made. After the assay of these fractions, separate and combined, saponins and chlorophyll were eliminated and the resulting extracts were stabilized.

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*From the Research Division of the CUP Laboratories—Bogotá.
**Professor at the Medical School of the Javeriana University.

The extract was concentrated (1 ccm. = 0.05 gram Folia Digitalis). Before each experiment this concentrate was diluted in physiological salt solution (NaCl 0.85%, KCl 0.01%, $CaCl_2$ 0.02%, $NaHCO_3$ 0.02%) thus forming a solution in which one cubic centimeter of infusion equalled 0.005 gram Folia Digitalis.

2. Practically all the experiments were made with cats which weighed between 1.7 kilograms and 3.0 kilograms. Of the total 86 cats used seven weighed over 3.0 kilograms and seven weighed under 1.7 kilograms.

3. All experiments were made under general anesthesia using the sodium salt of methyl-butyl-phenylbarbituric acid in 10% water solution. Four subcutaneous or intramuscular injections in different parts of the body were made, totally 0.5 ccm. for one kgm. of cat.

4. Thirty minutes after the injections the cats were under the anesthesia and could be safely handled.

5. The saphena vein was then dissected and a cannula, connected to a burette, was inserted in the vein.

6. A respiratory cannula was then introduced into the trachea or nose.

7. An arterial cannula, filled with anti-coagulant solution (Heparin or Sodium Citrate), was then introduced into the carotid artery and connected to a manometer.

8. The manometer oscillation and respiratory movements were registered on a kymograph. A chronograph recorded the time on the graphical record.

9. The infusion of the Digitalis solution was made slowly, one cubic centimeter per minute. Our experiments showed that from forty to sixty cubic centimeters of 0.5% solutions of Digitalis would kill the animal.

10. The criterion of de Lind van Wijngaarden (2) was followed, i. e., the number of experiments completed should be such that the difference in per cent does not exceed the limit of error $= 6.67 \times \sqrt{n-1}$ exceeds the limit ($6.67 \times \sqrt{n-1}$) then ten cats should be used. (n = number of cats used for each assay). Three was the minimum number of cats used for each assay. If the error in three cats

In some of experiments the registration of arterial pressure was omitted because the end of the experiment is determined by a sharp fall of the respiratory curve.

Results

TABLE I

DIGITALIS PURPUREA OF BOGOTÁ
Leaf collected in May. Alcoholic extract

No.	Cat weight in kgm.	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	1.7	0.167	0.0985		2.4		
2	2.6	0.240	0.0923		4.8		
3	2.5	0.250	0.1000		4.5		
4	2.9	0.310	0.1060		9.2		
5	3.0	0.300	0.1000		4.5		
6	2.3	0.176	0.0760		20.8		
7	2.0	0.210	0.1050		9.1		
8	1.7	0.175	0.1000		4.5		
9	1.7	0.175	0.1000		4.5		
10	3.3	0.276	0.0836	0.0961	13.0	7.73	20.0

Lethal dose of the examined powder for kilo cat ..... 96.1 mgm.
Difference from the International Standard 1928 ..... + 4.0%

TABLE II

DIGITALIS PURPUREA OF BOGOTÁ
Leaf Collected in May. Aqueous extract

No.	Cat weight in kgm.	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	1.9	0.2125	0.110		1.8		
2	2.2	0.2400	0.101		6.5		
3	3.0	0.3750	0.125		15.7		
4	3.0	0.2920	0.097		10.0		
5	2.9	0.3200	0.110		1.8		
6	3.7	0.4000	0.108	0.108	0	5.97	14.9

Lethal dose of the examined powder for kilo cat ..... 108.0 mgm.
Difference from the International Standard 1928 ..... −7.4%

TABLE III

DIGITALIS PURPUREA OF BOGOTÁ
Leaf collected in May. Alcoholic + aqueous extract

No.	Cat weight in kgm.	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	3.0	0.297	0.099		1.0		
2	2.3	0.235	0.102		2.0		
3	2.4	0.240	0.100	0.100	0	1.0	9.43

Lethal dose of the examined powder for kilo cat ..... 100.0 mgm.
Difference from the International Standard 1928 ..... 0.0%

TABLE IV

DIGITALIS PURPUREA OF BOGOTÁ
Leaf collected in May. Glycerinic extract

No.	Cat weight in kgm.	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	2.6	0.296	0.1130		4.7		
2	2.7	0.237	0.0948		14.0		
3	3.0	0.350	0.1160	0.1079	7.5	8.7	9.43

Lethal dose of the examined powder for kilo cat ..... 108.0 mgm.
Difference from the International Standard 1928 ..... —7.4%

TABLE V

DIGITALIS PURPUREA OF BOGOTÁ
Leaf collected in May. Alcoholic + aqueous extract (stable)

No.	Cat weight in kgm.	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	1.6	0.211	0.1318		26.7		
2	2.0	0.200	0.1000		3.9		
3	1.7	0.200	0.1230		18.2		
4	3.7	0.370	0.1000		3.9		
5	4.1	0.380	0.0927		10.9		
6	1.6	0.170	0.1089		4.7		
7	1.5	0.155	0.1000		3.9		
8	2.4	0.240	0.1000		3.9		
9	3.0	0.250	0.0833		20.0		
10	2.7	0.270	0.1000	0.104	3.9	10.0	20.0

Lethal dose of the examined powder for kilo cat ..... 104.0 mgm.
Difference from the International Standard 1928 ..... —3.9%

TABLE VI

DIGITALIS PURPUREA OF BOGOTÁ
Leaf collected in November. Aqueous extract

No.	Cat weight in kgm.	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	2.2	0.250	0.113		6.6		
2	3.3	0.352	0.107		0		
3	2.0	0.200	0.100	0.106	5.7	4.1	9.43

Lethal dose of the examined powder for kilo cat ..... 106.0 mgm.
Difference from the International Standard 1928 ..... —5.9%

TABLE VII

DIGITALIS PURPUREA OF BOGOTÁ
Leaf collected in November. Alcoholic extract

No.	Cat weight in kgm.	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	1.6	0.156	0.0975		3.7		
2	1.6	0.143	0.0893		5.0		
3	2.4	0.229	0.0954	0.094	1.5	3.4	9.43

Lethal dose of the examined powder for kilo cat ..... 94.0 mgm.
Difference from the International Standard 1928 ..... + 6.0%

TABLE VIII

DIGITALIS PURPUREA OF BOGOTÁ
Leaf collected in February and March. Alcoholic extract

No.	Cat weight in kgm.	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	2.1	0.182	0.0867		10.7		
2	1.7	0.174	0.1020		5.1		
3	3.2	0.306	0.0956		1.5		
4	2.7	0.276	0.1020		5.1		
5	2.1	0.1825	0.0869		10.7		
6	2.7	0.2325	0.0861		11.3		
7	1.5	0.164	0.1090		12.3		
8	2.0	0.200	0.1000		3.0		
9	1.9	0.1740	0.0915		5.7		
10	2.0	0.1960	0.0980		1.0		
11	1.7	0.1660	0.0976		0		
12	2.7	0.2650	0.0980		1.0		
13	2.6	0.2570	0.1000		3.0		
14	3.0	0.315	0.1050	0.097	8.2	5.6	24.0

Lethal dose of the examined powder for kilo cat ..... 97.0 mgm.
Difference from the International Standard 1928 ..... 3.0%

TABLE IX

DIGITALIS LANATA OF BOGOTÁ
Leaf collected in November. Aqueous extract

No.	Cat weight in kilo	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	2.1	0.250	0.118		0		
2	2.5	0.276	0.110		6.0		
3	4.0	0.530	0.130	0.117	11.0	5.7	9.43

Lethal dose of the examined powder for kilo cat ..... 117.0 mgm.

TABLE X

DIGITALIS LANATA OF BOGOTÁ
Leaf collected in November. Alcoholic extract

No.	Cat weight in kilo	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	2.2	0.207	0.0943		5.5		
2	2.1	0.230	0.1090		9.3		
3	1.9	0.180	0.0947	0.0997	5.0	6.6	9.43

Lethal dose of the examined powder for kilo cat ..... 99.7 mgm.

TABLE XI

"DIGITALIS REFERENCE STANDARD U. S. P. 1942", No. 0065 x 295972
Aqueous extract. 16-18. III. 1943

No.	Cat weight in kilo	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	1.8	0.276	0.1533		0		
2	2.8	0.415	0.1482		3.3		
3	1.9	0.300	0.1578	0.1531	3.1	3.1	9.43

Lethal dose of the examined powder for kilo cat ..... 153.1 mgm.
Difference from the powder of Digitalis of Bogotá..... —41.6%

TABLE XII

"DIGITALIS REFERENCE STANDARD U. S. P. 1942", No. 0065 x 295972
Alcoholic extract. 16-18. III. 1943

No.	Cat weight in kilo	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	2.2	0.3200	0.1454		9.3		
2	2.5	0.3875	0.1550		2.5		
3	2.1	0.3730	0.1776	0.159	10.5	7.43	9.43

Lethal dose of the examined powder for kilo cat ..... 159.0 mgm.
Difference from the powder of Digitalis of Bogotá (alc. extract) ..... —66.5%

TABLE XIII

"DIGALEN-ROCHE" (FOR INJECTIONS) No. 0.002-406061
Declared potency: 1 ccm. of the solution = 0.05 g. Fol. Digit. Agosto 1942

No.	Cat weight in kilo	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	2.8	0.331	0.118		0		
2	2.5	0.288	0.115		2.6		
3	2.5	0.302	0.121	0.118	2.6	1.4	9.43

Lethal dose of the examined preparation (calc. in powder) for kilo cat .... 118 mgm.
Difference from the alcoholic extract of the Digitalis of Bogotá ..... —23.8%

TABLE XIV

DIGITALIS PURPUREA POWDER, "LILLY", No. 5080-280163

No.	Cat weight in kilo	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	1.7	0.1887	0.111		13.3		
2	2.3	0.3170	0.137		7.0		
3	2.6	0.3590	0.138	0.128	7.0	9.0	9.43

Lethal dose of the examined powder for kilo cat ..... 128.0 mgm.
Difference from the aqueous extract of the Digitalis of Bogotá ..... —25.0%

TABLE XV

DIGITALIS PURPUREA POWDER, "LILLY", No. 5080-280163
Alcoholic extract. January 1943

No.	Cat weight in kilo	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	2.5	0.258	0.103		7.0		
2	2.5	0.282	0.112		2.0		
3	2.7	0.310	0.115	0.110	5.0	4.7	9.43

Lethal dose of the examined powder for kilo cat ..... 110.0 mgm.
Difference from the alcoholic extract of the Digitalis of Bogotá ..... —24.8%

In order to obtain some information on the possible influence of altitude in Bogotá (elevation 2640 meters above sea level), the experiments were repeated in Girardot (elevation 326 meters above sea level).

TABLE XVI

DIGITALIS PURPUREA OF BOGOTÁ
Purified total extract. Assay in Bogotá

No.	Cat weight in kilo	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	2.0	0.120	0.60		5.4		
2	1.4	0.110	0.079		24.6		
3	3.0	0.180	0.060		5.4		
4	2.0	0.117	0.058		8.5		
5	1.7	0.103	0.060	0.0634	5.4	9.8	13.3

Lethal dose of the examined powder for kilo cat ..... 63.4 mgm.

TABLE XVII

DIGITALIS PURPUREA OF BOGOTÁ
Purified total extract. Assay in Girardot

No.	Cat weight in kilo	Lethal dose of leaf in gram	Lethal dose leaf in gram for kilo cat	Average gram leaf by kilo cat	Difference in % from the average	Average of the difference	Permitted error of the difference from the average
1	1.6	0.150	0.0933		25.2		
2	2.4	0.170	0.0708		5.1		
3	1.5	0.115	0.0770		3.2		
4	2.7	0.175	0.0648		13.2		
5	1.7	0.120	0.0706		5.2		
6	1.65	0.116	0.0703		5.4		
7	2.40	0.165	0.0687		7.9		
8	2.97	0.240	0.0814	0.0746	9.1	9.3	17.6

Lethal dose of the examined powder for kilo cat ..... 74.6 mgm.
Difference from the potency obtained in Bogotá ..... — 15.2%

General Summary and Conclusions

I.—Digitalis purpurea from Bogotá, Colombia, has the same potency as the International Standard 1928, i. e., the minimal lethal dose for cats is 0.1 gram powdered leaf per kilogram weight of cat.

II.—Digitalis purpurea from Bogotá shows no influence due to the different annual seasons.

III.—Digitalis lanata from Bogotá has a minimal lethal dose of 0.1 gram powdered leaf per kilogram weight of cat.

IV.—Under identical conditions of extraction and biological determination, "Digitalis Reference Standard U. S. P. 1942" has a M. L. D. of 0.153 gram and 0.159 gram powdered leaf per kilogram weight of cat. The Standard powder is therefore 50% to 60% less active than the one obtained from Digitalis purpurea from Bogotá.

V.—Under identical condition "Digalen-Roche" has a M. L. D. of 0.118 gram Folia Digitalis per kilogram weight of cat.

VI.—Powder of Digitalis purpurea "Lilly" was found to have a M. L. D. of 0.128 and 0.110 gram per kilogram weight of cat.

VII.—The M. L. D. of Colombian Digitalis purpurea was found to be 14% more toxic in Bogotá (2640 meters above sea level) than in Girardot (326 meters above sea level). This difference could be explained by possible increased sensitivity to Digitalis due to the altitude.

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AROMATIC ELIXIR

By P. Robert Rasanen and Joseph B. Burt

AROMATIC ELIXIR has long been the subject of much study by workers with the object of reducing the time required for its preparation and improving its appearance, flavor, and odor. Its wide use as a vehicle and masking agent, and the fact that it is used in considerable quantities in prescription compounding fully justifies the attention which it has received. The chief difficulty encountered in the preparation of the elixir is in securing a clear finished product. The procedure in the U. S. P. XI is long and tedious and very trying on the pharmacist's patience. Even after repeated filtration, it is almost impossible to obtain a clear preparation. Our purpose was to compare the methods already proposed by others and to attempt to find a method which would do away with the repeated filtration and still yield a preparation with a flavor equal to that of the elixir official in the U. S. P. XI.

History

An elixir similar to the present U. S. P. XI Aromatic Elixir was introduced into the U. S. P. of 1880 under the title Elixir of Orange. The formula required one part of oil of orange to 100 parts of sugar in a one to three alcohol-water mixture, with cotton as the filtering medium. In the U. S. P. of 1890 compound spirit of orange was substituted for the oil and precipitated calcium phosphate was used as the filtering agent. In the U. S. P. VIII formula the filtering agent was changed to purified talc and the other ingredients remained unchanged. This U. S. P. VIII formula has remained official up to and including the U. S. P. XI.

Work has been done on this preparation since 1871 (1) when the Newark Pharmaceutical Association proposed a formula for an elixir. A complete survey and review of the literature of this preparation prior to 1934 was made by Lee and Close (2). They presented their review of the literature under the following headings:

1. Flavoring Substances
2. Alcohol and Sugar Content
3. Filtering Agents
4. Methods of Preparation

They also proposed a formula in which the compound spirit of orange was mixed with the purified talc by trituration and water was added in small portions and mixed frequently during fifteen minutes and the mixture filtered. The sugar was dissolved in the filtrate and the desired amount of alcohol added last. Their reasons for advocating the formula were as follows:

1. The time required to prepare the elixir was approximately one-tenth of that necessary for the present official elixir.
2. The alcoholic strength may be varied at will without modifying the technique of preparation.
3. The preparation is always a clear product, regardless of a variation in the alcoholic content.

During the same year, Havenhill and Smolt (3) proposed a method of making a soluble compound spirit of orange from either the U. S. P. X compound spirit of orange or directly from the oils of orange, lemon, coriander, and anise. This soluble spirit was then used to make the Aromatic Elixir by simply mixing. They maintained that the terpenes present in the aromatic oils of the compound spirit of orange were insoluble in the dilute alcohol used and that this was the cause of the chief difficulty arising in the preparation of the elixir. Their belief was that the oxygenated principles of the oils were the desirable constituents, but did not cause the cloudiness which results in preparing the U. S. P. XI elixir.

As a result of the study of Havenhill and Smolt, Smith and Burlage (4) suggested the use of terpeneless oils, which had previously been proposed by Jones (5) in 1922. Smith and Burlage prepared two samples of a soluble compound spirit of orange, using terpeneless oils of orange and lemon, with oil of anise and coriander. In one sample they replaced the oils of lemon and orange in the U. S. P. X formula with like volumes of the corresponding terpeneless oils, and in the other, since the terpeneless oils were much richer in flavoring principles than the official oils, one-tenth of the amounts of the terpeneless oils were used. These spirits were then used in preparing Aromatic Elixir by the official procedure, except that the filtration with purified talc was omitted. The resulting product was slightly opalescent, so it was filtered through a hard filter paper. Usually only one filtration was necessary. They found the product to be brilliantly clear and to have a delightful odor and taste which

might be varied in degree by using variable amounts of the new soluble compound spirit. Bibbins (6) objects to the use of terpeneless oils. He states that the terpeneless oils lack the delicate aromatic flavor which can be obtained from fresh oils of lemon and orange. Lockie (7) also did some work with terpeneless oils and suggested a formula for a compound spirit of orange and Aromatic Elixir in which the terpeneless oils were used. He stated that according to Fritzsche Brothers the terpeneless oils had the following relationship to the U. S. P. oils with reference to their use as flavors:

Terpeneless Oil of Orange = 35 or 40 to 1.
Terpeneless Oil of Lemon = 16 to 1.

Lockie took this into consideration when suggesting his formula for the compound spirit of orange containing the terpeneless oils. Smith and Burlage (4) had used one-tenth the amount specified in the formula for compound spirit of orange for each oil, and then complained, according to Lockie, that the taste was too orange-like. Lockie suggested the formula below, which he thought had a flavor superior to that of the present U. S. P. XI elixir. He used the terpeneless oils in the proportion suggested by Fritzsche Brothers, i. e., one-fortieth the prescribed quantity of oil of orange and one-sixteenth the prescribed quantity of oil of lemon.

Oil of Orange, Terpeneless	5 cc.
Oil of Lemon, Terpeneless	3 cc.
Oil of Coriander	20 cc.
Oil of Anise	5 cc.
Alcohol, a sufficient quantity	
To make	1000 cc.

In the experimental work which follows, the elixir was prepared according to the various proposed formulas and the resulting products were compared with the product obtained according to the present U. S. P. XI formula for Aromatic Elixir. The factors considered were (a) time consumed in the preparation, (b) flavor and odor of the finished product, and (c) appearance of the preparation. In every instance Eaton and Dikeman No. 613 filter paper was used.

Experimental

Method I: The U. S. P. XI procedure was carried out in order that the procedure, qualities of the product, and time consumed in the operation might be used as the basis for comparison with the results obtained with the proposed methods.

The filtrate had to be repeatedly returned to the filter paper during a two-day period before an acceptable product was obtained and even then the product was not absolutely clear. The method was repeated several times and in every instance the results were identical.

Method II: In 1917 Cook (8) made the following statement concerning Aromatic Elixir: "It is unfortunate that the purified talc, which is not a satisfactory filtering medium, was not replaced by purified siliceous earth (purified kieselguhr), which has been made official." Lee and Close (2) made the statement that purified siliceous earth not only speeds the rate of filtration, but produces a clear filtrate promptly. However, Havenhill and Smolt (3) maintained that in actual experience purified talc has been found to be the most satisfactory filtering medium. With these statements in mind the U. S. P. XI procedure was again followed, but this time purified siliceous earth was substituted for the purified talc. The results were almost identical with those obtained under Method I.

Method III: The U. S. P. XI procedure was modified by triturating the compound spirit of orange with the purified talc and then adding to this the previously mixed alcohol, water, and syrup in small portions with stirring. This mixture was then mixed frequently during a period of fifteen minutes and finally filtered through a wetted filter paper.

This method gave a clear product the first time through the filter paper, but the complete filtration required from eight to twelve hours. This procedure is almost identical with the method proposed by Gibson and Parker (9) except that their formula required 10 cc. less of alcohol. Purified siliceous earth was substituted for purified talc and the resulting product was clear the first time through the filter paper and there was no appreciable difference in the time required for filtration.

Method IV: This method was proposed by Lee and Close (2).

Compound Spirit of Orange	12 cc.
Purified Talc	30 Gm.
Sugar	320 Gm.
Alcohol, the desired amount,	
Distilled Water, a sufficient quantity,	
To make	1000 Gm.

Carefully mix the compound spirit of orange and purified talc by trituration. Add about 800 cc. of water, in convenient proportions, and triturate after each addition. Agitate frequently for about fifteen minutes and filter in the usual manner. Dissolve the sugar in 550 cc. of the clear filtrate and to it add the amount of alcohol desired. Finally make up to 1000 cc. with the required amount of the clear filtrate.

The first 10 cc. of the filtrate had to be returned to the filter paper and the complete filtration required about thirty minutes. Only a few more minutes were required to complete the preparation.

Method V: This method includes the two suggestions made by Havenhill and Smolt (3) for preparing a soluble compound spirit of orange.

(a) Soluble Compound Spirit of Orange

Compound Spirit of Orange (U. S. P. X)	640 cc.
Purified Talc	30 Gm.
Distilled Water	365 cc.

Mix the liquids in a large separatory funnel, shake thoroughly, and allow to stand one-half hour. Draw off the cloudy lower liquid, thoroughly mix it with the talc, and filter in the approved manner to secure a clear filtrate and to restrict evaporation.

By this method a preparation was obtained which was clear and had a distinct yellow color. When preparing 100 cc. of the soluble spirit, only 4 cc. of the 17.6 cc. of oils present in the compound spirit of orange used were taken up by the lower cloudy layer. There was a loss of 13.6 cc. of oils which is approximately 77 per cent of total volume of volatile oils present. Further consideration of this loss is taken up under the following procedure.

(b) Soluble Compound Spirit of Orange

Oil of Orange	128	cc.
Oil of Lemon	32	cc.
Oil of Anise	3.2	cc.
Oil of Coriander	12.8	cc.
Alcohol	465	cc.
Water	370	cc.
Purified Talc		
To make about	750	cc.

Mix the liquid thoroughly in a separatory funnel of suitable size, and allow to stand one-half hour. Draw off the cloudy lower liquid, mix it with the talc, and filter in the approved manner to secure a clear filtrate and to restrict evaporation.

This procedure also gave a clear filtrate the first time through the filter paper and gave a distinctly yellow liquid. When a 100 cc. sample was prepared, rough measurements showed that only about 3.5 cc. of the oils were in the bottom layer and 20 cc. were thrown away. This loss of oils was 85 per cent of the total volume of oils used. If the mixture were allowed to separate out completely, only 0.4 cc. of the oils was taken up by the bottom layer. It was thought at this point that such a great loss of oils might be avoided by using proportionally smaller amounts of each oil, but the results indicated that smaller amounts of oils were being taken up by the lower layer. It was noted that if the water were added to the mixture of alcohol and oils last somewhat less separation took place in the half-hour period, but this was thought to be insignificant since the amount of separation was the same in every case if the mixtures were allowed to stand until completely separated.

By this procedure a portion of the oils in the lower cloudy layer is lost also, but assuming the loss to be that which may be measured (85 per cent), it appears that by this method an excessive amount of oils is wasted. However, if one studies the matter more closely, this loss may not be much greater than that experienced using the U. S. P. XI method for preparing Aromatic Elixir. By the method of Havenhill and Smolt, 176 cc. of oils are required to prepare about 750 cc. of the soluble compound spirit of orange. The U. S. P. XI formula required that 275 cc. of the oils be used in making 1000 cc. of the

spirit. If the same amount of oils is used in the Havenhill and Smolt formula for the soluble spirit then about 1183 cc. of the spirit should be obtained. Since the formula of Havenhill and Smolt for Aromatic Elixir required 16 cc. of this soluble spirit to make 1000 cc. of Aromatic Elixir, then 1183 cc. of the soluble spirit would make approximately 73,937 cc. of elixir. Since it was roughly estimated that there was a loss of 85 per cent of the oils used, then 85 per cent of 275 equals 234 cc., which is the amount of oils lost in preparing 73,937 cc. of Aromatic Elixir. Obviously the loss of oils in preparing 1000 cc. of Aromatic Elixir by the U. S. P. formula is not apparent since only 12 cc. of the U. S. P. spirit are used. If 12 cc. of the U. S. P. spirit is sufficient to prepare 1000 cc. of Aromatic Elixir, then 1000 cc. of the U. S. P. spirit will make 83,333 cc. of the elixir. Therefore, the loss of oils experienced in preparing 1183 cc. of the soluble spirit by the Havenhill and Smolt method should be compared to the loss of oils which takes place in preparing 83,333 cc. of Aromatic Elixir by the U. S. P. procedure. The loss here would of course be more apparent since much is lost in the filtration process. Unfortunately, this volume cannot be measured since the quantity taken up on the surface of the purified talc and that lost by evaporation cannot be determined. However, anyone who has prepared Aromatic Elixir by the U. S. P. method can well imagine that the loss would be considerable and would compare within reasonable limits with that lost by the Havenhill and Smolt method.

Havenhill and Smolt (3) determined the amount of oils or compound spirit of orange needed to prepare a soluble spirit of orange so that when 16 cc. of this soluble compound spirit of orange were used to prepare 1000 cc. of Aromatic Elixir it would contain the same amount of oxygenated principles as that contained in the elixir prepared by the U. S. P. XI procedure. This was done by the comparisons of color produced by a *m*-phenylenediamine reagent prepared according to the method given in Official and Tentative Methods of Analysis of the Association of Official Agricultural Chemists (10). This same method was attempted in the laboratory, but the colors produced were not of sufficient intensity to be differentiated by means of a colorimeter. The difficulty may have been that the *m*-phenylenediamine hydrochloride used was prepared in the laboratory from *m*-phenylenediamine. The sulfite-fuchsin method was tried on known samples of citral, but the colors produced did not vary according to

the amount of aldehydes present. Havenhill and Smolt also found this to be unsatisfactory.

The soluble compound spirit of orange was used in making Aromatic Elixir by the following formula which was proposed by Havenhill and Smolt.

AROMATIC ELIXIR

Compound Spirit of Orange, Soluble	16 cc.
Syrup	375 cc.
Alcohol	250 cc.
Distilled Water	380 cc.
To make about	1000 cc.

Mix the soluble compound spirit of orange with the alcohol. Add the syrup in small portions, mixing well after each addition; then in like manner add the distilled water. The product at this stage is full of minute bubbles, but clears in a few minutes. This procedure gave a clear elixir by simple mixing.

Method VI: This formula was proposed by Lockie (7) and consists of substituting terpeneless oils of orange and lemon for the U. S. P. oils of orange and lemon. The relationship of the terpeneless oils to the U. S. P. oils, as indicated previously, was taken into consideration in the following formula for making compound spirit of orange.

Oil of Orange, Terpeneless	5 cc.
Oil of Lemon, Terpeneless	3 cc.
Oil of Coriander	20 cc.
Oil of Anise	5 cc.
Alcohol, a sufficient quantity,	
To make	1000 cc.

The oils were mixed and the alcohol was added to the mixture of oils.

This procedure gave a cloudy preparation and upon using each oil separately in the same quantity of alcohol it was found that the terpeneless oil of orange was the cause of the cloudiness. However, on standing over night the preparation was filtered and a clear spirit obtained.

This compound spirit of orange was then used in the U. S. P. XI formula for Aromatic Elixir and a clear preparation was obtained if care were used in mixing the spirit with the alcohol, syrup, and water. The alcohol was added first, followed by the syrup in small portions, mixing well after each addition; then enough water was added in a similar manner to make the required volume.

The elixir was prepared many times by this method, but often the resulting product had a slight haziness which could easily be removed by simply passing through a hard wetted filter paper. The variation in results may have been due to the changes in room temperature. The compound spirit of orange prepared from terpeneless oils is cloudy upon mixing due to the terpeneless oil of orange. However, this is no disadvantage over the U. S. P. XI compound spirit of orange since it cannot be prepared clear by simple mixing. Here again the oil of orange is the cause of the cloudiness since it is not completely soluble in the alcohol. No mention is made of filtering compound spirit of orange in the U. S. P. XI even though a cloudy preparation is always obtained.

The Aromatic Elixir obtained from the terpeneless oils had a somewhat predominating odor of coriander. Larger amounts of the compound spirit of orange might be used, thereby giving more flavor in the elixir if desired.

Method VII: The quantities of ingredients used in this procedure were the same as those in the U. S. P. XI formula except that 318 grams of sugar and a sufficient quantity of water were substituted for the syrup. The compound spirit of orange was triturated with the talc and 250 cc. of alcohol and 600 cc. of water previously mixed were added in small portions, mixing after each addition. The mixture was then filtered. The sugar was dissolved in the filtrate by agitation and the solution made up to 1000 cc. with a 1 in 4 alcohol and water mixture.

The purpose of substituting the sugar for the syrup was to decrease the viscosity of the liquid being filtered. This had been suggested by Lee and Close (2), but they added the alcohol last. They believed that the flavor was not impaired by lower alcohol content or by adding the alcohol last. Flavor tests, which are shown below, showed very little difference in the elixir made by this method and the one proposed by Lee and Close (Method IV) when the elixirs themselves were used. It was believed that the high alcoholic content

made it difficult to distinguish between the two. However, when the elixirs were diluted with four volumes of water the odor and flavor of the elixir prepared by Method VII were noticeably stronger than those prepared by Method IV. The filtration required about thirty to forty-five minutes and the filtrate came through clear after the first few cc. had been returned to the filter paper.

Table I shows the comparative rating of the elixirs prepared by the methods just described. They were compared for flavor, odor, time consumed in preparation, and appearance. Since a difference in flavor and odor could not be distinguished in the full-strength elixirs because of the alcoholic content, they were diluted with 4 parts of water. The numbers used to indicate the relative values are arbitrarily assigned, the value 1 indicating the most satisfactory product from the standpoint of flavor or odor, and the shortest period of time required for its preparation.

TABLE I

Method	Flavor on Dilution 1 to 4	Time consumed in Preparation	Odor on Dilution 1 to 4	Appearance
I	1	5	2	clear
II	2	5	2	clear
III	2	4	2	clear
IV	4	3	4	clear
V	2.5	1	2.5	clear
VI	1	2	1	clear
VII	2	3	2	clear

Conclusions

Table I indicates that Method VI gives the best elixir for flavor and taste and it ranks second in the time consumed in preparation. The time of preparation varies since sometimes it is clear upon simple mixing, while occasionally it has a very slight haziness and must be filtered. However, on the average, the time consumed is only slightly more than that required in Method V. It is commonly believed, however, that the Revision Committee of the Pharmacopœia has not accepted the use of terpeneless oils or terpeneless extracts since they lack uniformity and no set of standards has been issued for them. Since these are coming into common use and are reasonably priced, there is a possibility that these standards might easily

be established. Should this be the case, then the method requiring the terpeneless oils would be far superior to any of the other methods proposed.

The method of Havenhill and Smolt (Method V) ranks second in our estimation. There is an apparent loss of the oils by this method, but as was pointed out previously, a similar loss is experienced by the U. S. P. procedure. However, this loss experienced in preparing the elixir by the U. S. P. procedure is not so apparent unless one stops to reason the matter out. It was our opinion that their elixir lacked flavor when compared to the U. S. P. XI Aromatic Elixir, but this difference was slight.

Should neither of these methods gain the approval of the Revision Committee of the Pharmacopœia of the United States, then we recommend Method VII, which consists of triturating the compound spirit of orange with the purified talc, adding the previously mixed water and alcohol in small portions with constant agitation, filtering, and then dissolving the required amount of sugar in this clear filtrate and bringing the product up to the desired volume with an alcohol-water mixture.

In our estimation the elixir prepared by Method IV, which was proposed by Lee and Close (2), lacked flavor when compared in diluted form to the U. S. P. XI elixirs of a similar dilution. Method II requires an over night filtration, but gives a clear preparation without the repeated filtrations that are required by the U. S. P. method.

Summary

Various methods for preparing Aromatic Elixir were compared to the U. S. P. XI procedure. The finished products were compared for flavor, odor, appearance and time consumed in preparation, and ranked accordingly. An elixir prepared by a formula requiring the use of a soluble compound spirit of orange prepared from terpeneless oils of orange and lemon was found to be the most satisfactory. This formula was originally proposed by Lockie. A formula requiring the use of a soluble compound spirit of orange proposed by Havenhill and Smolt ranked a close second. Another formula in which sugar and water were substituted for the syrup was found to rank third. A similar formula proposed by Lee and Close lacked flavor. Other modifications of the U. S. P. formula were tried which

consisted of triturating the compound spirit of orange with the purified talc or purified siliceous earth, but the only advantage of these methods over the U. S. P. XI formula was that the filtrate was clear the first time through the filter paper.

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SAPONATED SOLUTION OF CRESOL

By P. Robert Rasanen and Joseph B. Burt

THE U. S. P. XI method for making Saponated Solution of Cresol has received considerable criticism from pharmacists. The chief difficulty is in the length of time required to effect complete saponification of the linseed oil, which often takes several hours. Objection is also made because the directions provide that the cresol be mixed with the linseed oil before saponification, which is carried out by the aid of heat. As a result of this procedure, the room becomes filled with cresol vapors. In addition, the application of heat results in the loss of some of the cresol.

History

Saponated Solution of Cresol first appeared in the U. S. P. VIII. The following table shows the various changes in the formula of this preparation since it first appeared in the U. S. P.

	U. S. P. VIII	U. S. P. IX	U. S. P. X	U. S. P. XI
Cresol	500 Gm.	500 Gm.	500 cc.	500 cc.
Linseed Oil	350 Gm.	300 Gm.	350 cc.	350 cc.
Potassium Hydroxide	80 Gm.	80 Gm.	22 cc.*	14.52 Gm.
Sodium Hydroxide	—	—	88 cc.*	37.05 Gm.
Alcohol	—	30 cc.	—	—
Water, a sufficient quantity				
To make	1000 Gm.	1000 cc.	1000 cc.	1000 cc.

*In this case a dekanormal solution was used.

According to the U. S. P. VIII, the oil, cresol, and an aqueous solution of potassium hydroxide were mixed and heated with stirring until a clear solution resulted. The formula of the U. S. P. IX required that the oil be heated to 70° C., that an aqueous solution of 80 grams of potassium hydroxide be added and mixed thoroughly followed by 30 cc. of alcohol, and the mixture heated without stirring until a small portion is found to be soluble in boiling water. Then the cresol was added, keeping the mixture at 70° C. In the formula of the U. S. P. X the alcohol was omitted and dekanormal solutions of sodium and potassium hydroxides were used. These solutions were added to the linseed oil and cresol, previously mixed, and the

mixture was heated to 70° C., until a portion of the solution gave a clear solution with nine volumes of cold distilled water. The U. S. P. XI formula was similar to that of the U. S. P. X except that sodium and potassium hydroxides replaced the dekanormal solutions.

Experimental investigation of this solution has been reported as early as 1906. LaWall and Cook (1) prepared the solution by heating the linseed oil and potassium hydroxide solution at 70° C., in the presence of 40 cc. of alcohol until a portion gave a clear solution with boiling water. The cresol was then added and mixed until a homogenous preparation was obtained. Nitardy (2) offered a similar formula. Hilton (3) suggested substituting oleic acid for the linseed oil and saponifying the acid with sodium hydroxide in the presence of the cresol. Mueller (4) suggested substituting cottonseed oil for the linseed oil and saponifying this with potassium hydroxide solution in the presence of alcohol. In 1920, Gray (5) suggested using equal parts, by weight, of soft soap and cresol. This same procedure was also suggested in 1924 by Griffith (6). In 1932, Berry and his students (7) found a method identical with that of Hilton's to be the most satisfactory. In 1936, Smith and Burlage (8) suggested Gray's method, using soft soap. They prepared the solution by two methods: (a) by heating to 70° C.; and (b) by agitation; the time required was five minutes and six minutes, respectively. This was considerably shorter than the time required by Berry's and Nitardy's methods, which took nine and twenty minutes, respectively.

Various formulas were again suggested for the U. S. P. XII, Beal and Zopf being the chief contributors. Their methods were very similar to those already mentioned, such as using alcohol (9), substituting oleic acid for a portion of the oil (10), and using soft soap (11) instead of saponifying the oil. Various portions were prepared according to the methods proposed and the results were compared for the time consumed and the appearance of the preparation.

Experimental

Method I: Five hundred grams of soft soap were dissolved in 500 cc. of cresol. After solution was effected, water was added to make 1000 cc.

This method was somewhat slow and tedious because of the time consumed in dissolving the soft soap. Although this method would be acceptable if the soap and cresol were allowed to stand over night, it would not be satisfactory if the solution were required upon short notice. The use of a mechanical stirrer will speed the process of solution.

Method II:

Cresol	500	cc.
Linseed Oil	330	cc.
Oleic Acid	22	cc.
Potassium Hydroxide	72.58	Gm.
Distilled Water, a sufficient quantity,		
To make	1000	cc.

Mix the oil and the oleic acid in a vessel having a capacity of at least 2000 cc., heat the mixture to about 85° C., and add the potassium hydroxide, just previously dissolved in 500 cc. of distilled water. Mix thoroughly, preferably with a mechanical stirrer, and heat the mixture on a hot plate, continuing the stirring until a small portion dissolves in hot distilled water to form a clear solution. Incorporate the cresol by stirring until 1 cc. of the mixture forms a clear solution with 9 cc. of cold distilled water, cool the mixture, transfer it to a graduated vessel, and add sufficient distilled water to make the product measure, after mixing, 1000 cc.

This method gave complete saponification within about 5 or 6 minutes. However, it was thought that possibly the exclusive use of potassium hydroxide was the factor increasing the speed of saponification, rather than the use of the oleic acid. A proportionate sample of oil was treated with an aqueous solution of potassium hydroxide and saponification required about fifteen to twenty minutes, without the aid of heat. Similar soaps were made by using mixtures of potassium and sodium hydroxides, but very little difference in the time of saponification was noted. Potassium hydroxide alone gives a darker soap than a mixture of the two alkalies. It has been stated that a mixture of the two alkalies gives a better, softer soap, and that the addition of sodium hydroxide gives a soap which is more soluble.

Method III:

Cresol	500	cc.
Linseed Oil	350	cc.
Alcohol	55	cc.
Potassium Hydroxide	14.52	Gm.
Sodium Hydroxide	37.05	Gm.
Distilled Water, a sufficient quantity,		
To make	1000	cc.

Mix the linseed oil and the alcohol. Dissolve the potassium and sodium hydroxides in 100 cc. of distilled water and immediately add this solution to the oil-alcohol mixture. Stir thoroughly until saponification is complete. Then add the cresol and stir or shake until solution is complete. Add a sufficient quantity of distilled water to make the solution measure 1000 cc.

Isopropyl alcohol may be substituted for ethyl alcohol.

No heat was used in this method except that produced when the alkali was dissolved in water. Saponification was complete within one or two minutes, at which point a semisolid mass was formed upon stirring. This was dissolved in cresol. It was noted that the 50 cc. of distilled water, originally specified by Zopf (later corrected to read 100 cc., by a letter to committee members), was insufficient, since difficulty was encountered when this quantity was used. In some cases, several hours were required to dissolve the soap in cresol. When 100 cc. of water were used, the soap dissolved in a short time. When isopropyl alcohol was substituted for ethyl alcohol, no difference in the time of complete saponification was noted.

Method IV: The method of the U. S. P. XI was followed and saponification required several hours, and some foam was produced, with the result that a clear finished product was not obtained. A considerable amount of cresol was also lost by evaporation.

Conclusions

Of the four different methods and variations of these methods tried in the laboratory, Method III was without a question the superior. By this method, the pharmacist may prepare a portion of the solution upon a moment's notice. The only apparatus needed

is a beaker or graduate and a stirring rod. The preparation can be made within five or ten minutes, in such quantities as required, or the pharmacist can make up larger portions very conveniently during his spare time. No disagreeable odor of cresol is given off, and constant heating, stirring and watching are not required.

It is suggested, since this preparation is not used internally, that a tax-free alcohol, suitable for use in external preparations, be used in order to reduce the cost.

Summary

Saponated Solution of Cresol was prepared by three proposed methods which were compared to the U. S. P. XI procedure.

(1) Soft soap was substituted for the linseed oil and alkali.

(2) A small amount of oleic acid was added to the linseed oil before saponification.

(3) A small amount of alcohol was added to the oil before saponification.

Method (3), which was proposed by Zopf to the U. S. P. Committee, was found to be the best since complete saponification required only a few minutes without the aid of heat, and no loss of cresol took place.

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SELECTED ABSTRACTS

Chemical Side of Chemotherapy. E. H. Northey. *Ind. Eng. Chem. 35,* 829 (1943). The author places the origin of chemotherapy, the treatment of infectious diseases through specific chemical agents, as early in the sixteenth century when Jacob Carpensis discovered the beneficial effects of mercury in the treatment of syphilis. The discovery of the antimalarial activity of quinine and the development of arsphenamine as an antispyhilitic both involved chemotherapeutic agents which are antagonistic to protozoa.

The observation in 1911 that Optochin had a curative effect on pneumonia furnished the first example of antibacterial chemotherapy. The selective staining of different bacteria by dyes led to a search to find a dye which would kill bacteria in the blood stream without harm to the patient; the synthesis of Prontosil in 1932 opened the way for the preparation and investigation of the sulfonamides.

The nomenclature and classification of the sulfanilamide derivatives are considered briefly. Only a few of the approximately 2500 compounds of this type which have been described have been found suitable for clinical use.

Bell and Roblin have advanced a theory to explain the action of the sulfonamides which combines the knowledge of the inhibitory effect of *p*-aminobenzoic acid upon the bacteriostatic action of this group of drugs with additional observations. This involves consideration of physico-chemical and molecular structures, data for which was collected *in vitro* on the minimum molar concentration (CR) of the sulfonamide required to produce bacteriostasis of *E. coli* grown in a synthetic culture medium. According to this theory the most active sulfanilamide derivatives are those which approach most closely to the molecular structure and state of distribution of electric charge of the *p*-aminobenzoate ion.

Bell and Roblin have plotted a curve which shows a remarkable correlation of activities and dissociation constants in view of the experimental error in log $1/C_R$ of ± 0.3. They have mathematically developed their theory so that when the electronegativity of a group substituted for H on the N of the sulfamyl group ($—SO_2NH_2$) is known, the activity of the compound *in vitro* can be predicted.

Production problems encountered in the synthesis of sulfadiazine are described.

The future development of chemotherapy appears promising, especially since the essential metabolite theory of chemotherapeutic action has been found to be not limited to drugs in which *p*-aminobenzoic acid is the essential growth factor. For example, pantoyltauramide, in which the carboxyl group of pantothenic acid has been replaced by the sulfamyl group, has been shown to inhibit the growth of organisms requiring pantothenic acid for their metabolic processes; similarly, 3-sulfamylpyridine inhibits organisms requiring nicotinic acid.

Much research is being conducted also on the metabolic products of various molds; penicillin is a chemotherapeutic agent of this type.

Toxic Reactions to Succinylsulfathiazole. R. C. Clay and K. L. Pickrell. *J. A. M. A. 123,* 203 (1943). Throughout the literature reporting the use of this drug emphasis is placed on its freedom from toxicity. The authors agree that its use is attended by less frequent unfavorable reactions than is the case with sulfanilylguanidine, but point out that toxic manifestations occasionally occur.

The records of the Johns Hopkins Hospital showed that 100 adult patients had received succinylsulfathiazole for periods up to five weeks in the treatment of colonic carcinoma, diverticulitis, bacillary dysentery, accidental perforations of the bowel, ureterosigmoidostomy, chronic fecal fistula and rectovaginal fistula. In the majority of cases the dosage was 0.25 gm. per kg. as an initial dose and as a daily dose administered in six equal portions thereafter. A few patients received less than this, and several received much more.

In this series of cases only two patients exhibited unfavorable reactions: the first was a case of fever, rash and arthralgia, and the second was a case of crystalluria with hematuria. Brief case reports are presented concerning these two patients.

The authors recommend that frequent urinalyses be made during the administration of this drug. While anemia attributable to the drug was not observed, it is believed that frequent blood examinations are also indicated.

The Effect of Ultra-Violet Irradiation on the Vitamin A, Carotene, and Riboflavin Content of Milk. I. Fuhr, A. C. Dornbush and W. H. Peterson. *J. Dairy Sci. 26,* 643 (1943). Several investigators have previously reported that carotene, vitamin A, vitamin B_1 and riboflavin are either destroyed or inactivated partially or completely by prolonged exposure to ultra-violet light. Although no destruction of the first three of these principles has been reported in milk irradiated to produce 135 U. S. P. units of vitamin D per quart, the recent development of 400-unit milk was thought to make necessary the reinvestigation of this problem.

Two series of experiments were conducted, Series 1 being concerned with vitamin B_1 and Series 2 with carotene, vitamin A and riboflavin. The milk used in Series 1 was not pasturized; that used in Series 2 consisted of five different lots, two of which were market milks and the other three were from the same source as for Series 1. All of these milks had been irradiated and assayed at least 400 U. S. P. units of vitamin D per quart.

In Series 1 the rat-growth technic was used. It was found that growth ceased after a period of three weeks on a diet deficient in vitamin B_1. Thereafter for two weeks each of one group of rats received daily 10 cc. of untreated milk; each of a second group received the same amount of irradiated milk; and each of a third group received 3 micrograms of thiamine hydrochloride daily. In all cases these feedings were in addition to the basal ration. The growth response was similar among the groups, demonstrating that the vitamin B_1 content of milk is not reduced by irradiation to the strength of 400 U. S. P. units of vitamin D per quart.

In addition, the data on the rats which received thiamine hydrochloride confirms the observations of other investigators who have reported that cow's milk contains from 2 to 3 micrograms of this substance in each 10 cc.

In Series 2 carotene and vitamin A were extracted from the samples of milk by the method of Olson, Hegsted and Peterson, after which the two substances were measured spectrophotometrically. The value used in all calculations for vitamin A was $E\ \frac{1\%}{1\ cm.}\ 328\ m\mu = 1600$. The microbiological method of Snell and Strong was used to determine the riboflavin content of the milk.

It was found that the carotene, vitamin A and riboflavin content of milk was not diminished by irradiation to the strength previously

indicated. Samples of winter milk revealed lower values for carotene and vitamin A than summer milk, but this is a normal seasonal variation.

Sulfamerazine: Clinical Evaluation in 116 Cases. W. H. Hall and W. W. Spink. *J. A. M. A. 123,* 125 (1943). Sulfamerazine, which is chemically 2-sulfanilamido-4-methylpyrimidine, is the monomethyl derivative of sulfadiazine. The results obtained in the treatment of 116 patients with sulfamerazine or its sodium salt are reported.

In 40 cases of pneumococcic pneumonia or bronchitis sulfamerazine appeared to be as effective as sulfadiazine, and the same conclusion was drawn from the treatment of 33 cases of streptococcic infection. However, sulfathiazole was found superior to sulfamerazine in cases of staphylococcic sepsis. Two cases of meningitis due to type B influenza bacilli and three patients with meningococcic meningitis recovered following therapy with sulfamerazine. The drug was also used in the treatment of several infections of miscellaneous types.

Toxic manifestations encountered in the entire group were as follows: nausea and vomiting in 5 cases; drug fever in 3; dermatitis in 2; leukopenia and granulocytopenia in 1; gross hematuria and anuria in 1; and oliguria in 1. The drug caused less nausea and vomiting than sulfapyridine, and fewer skin eruptions and instances of drug fever than sulfathiazole. Despite the fact that sulfamerazine is two and one-half times as soluble in water as sulfadiazine, and that its acetylated form is almost twice as soluble in the same solvent as the comparable form of sulfadiazine, non-fatal urinary tract complications were caused by sulfamerazine in 2 cases. In both of these patients an extrarenal precipitation of crystals occurred which mechanically obstructed the free flow of urine. The intravenous administration of fluids, including sodium bicarbonate solution in 1 case, relieved this condition. On the basis of these and other observations, the authors recommend that the urinary output be maintained at 1000 to 2000 cc. per day, and that sodium bicarbonate should be given in amounts sufficient to raise the pH of the urine to 7.5 or more.

Modern Emulgents and Their Uses. W. Nixon. *Pharm. J.* 97, 103 (1943). Data are presented on a number of new emulsifying agents of British production, describing their properties and uses and listing their manufacturers. In some instances formulas for emulsions or for cosmetic creams are suggested.

Cellofas W. L. D. is said to be an ether of cellulose; it is cream-colored, fibrous in nature, and non-hygroscopic. Its aqueous solution is colorless, viscous, and neutral in reaction. By means of the solution O/W emulsions with oils, fats and waxes may be prepared.

Cellofas W. F. Z. is the sodium salt of a cellulosic acid and is soluble in both hot and cold water. It is hygroscopic in nature. A 5 per cent solution may be used in preparing O/W emulsions or as a thickening agent to prevent the creaming of emulsions.

Promulsin, another cellulose derivative, is said to be a polyose. It is a white, odorless powder and is best used in the form of a 3 per cent aqueous solution which may be diluted if desired.

Tylose S. L. 400 is believed to be another cellulose derivative, although its composition was not revealed by the manufacturer. At present it is not available, but Tylose C. 450 may be obtained for preparing solutions of a medium viscosity. It produces O/W emulsions.

P. M. B. 444 is a creamy, fibrous product concerning the chemistry of which no information was furnished. It is soluble in cold water, and may be used to prepare O/W emulsions, shaving creams, hair fixatives, etc.

Unemul, which occurs as a white paste, is a gelatinous form of hydrated aluminum oxide rendered insoluble in acids or alkalies by a process of ageing. It is recommended for use in preparing emulsions for internal use, and is resistant to attack by bacteria or fungi.

Manucol is a highly purified form of sodium alginate, and consists of a light, buff-colored powder containing 12 to 15 per cent of moisture in equilibrium. It is offered in types I, III, and V, the aqueous solutions of which exhibit increasing viscosity in the order named. At present it is not available for pharmaceutical purposes.

Lanette Wax S. X., which is a cream-colored product with a melting point of approximately 50° C., is said to be a sulfated cetyl-stearyl alcohol. It is self-emulsifiable with water, yielding an O/W emulsion; it gives the same type of emulsion with fixed oils, fats and waxes.

Cyclochem Wax E. M. 4/76 is white in appearance, self-emulsifying with water, and produces O/W emulsions. Another variety, Cyclochem Wax E. M. 3/76, is also white; it may be used to replace cetyl alcohol for the preparation of O/W or W/O emulsions.

Halden Emulsifying Bases (H. E. B.) are offered in a number of types: H. E. B., H. E. B. Co., H. E. B. protective normal, H. E. B. protective waterproof, and Lac H. E. B. They consist of paraffin bases with a balanced proportion of stable higher fatty alcohols and their esters. The bases are neutral and act as cleansing agents in both the oil and water phase.

Crembase, said to be an all-purpose emulsion wax, is a cream-colored product of firm consistence. It is recommended for use in vanishing creams.

Abracol G. S. P. and Abracol G. M. S. are wax-like substances and are said to be the equivalent of Tegin, Tegin P., etc. They are recommended for the manufacture of cosmetic creams and lotions.

All of the cellulose derivatives yield viscous solutions which do not ferment; however, emulsions in which they are incorporated may undergo fermentation, and for this reason the addition of a preservative such as sodium benzoate or one of the esters of *p*-hydroxybenzoic acid is desirable.

SOLID EXTRACTS

Seventy-five years ago the American Medical Association urged the cultivation of cinchona trees in the United States. Three memorials were submitted to Congress explaining the wisdom and need of a domestic source of quinine. After seven years of effort by a committee designated to interest our Government in this program, further steps to accomplish this end were abandoned.

AJP

One hundred and twenty-three years ago Pelletier and Caventou isolated quinine from cinchona. For years many other workers had sought to do this without success. For this great achievement they were awarded the Prix Monthyon which carried with it a prize of 10,000 francs. Years afterward the school children of France contributed their centimes and francs to erect a statue to these two great men.

AJP

Over 150,000,000 pounds of household fats have been salvaged during the past 12 months in the United States. In June collections totaled over 10,000,000 pounds. It is hard to realize that this fat was at one time thrown away by American housewives. The success of this program is largely due to the extremely effective campaign conducted by the country's newspapers and radio stations.

AJP

The forthright action of the Centaur Company in recalling all packages of Castoria that were on dealers' shelves last May has been commended by many trade and Government groups. The new product now available can be distinguished from the old by a green band on the packages. The experience with Castoria is another example of a profound effect produced by a seemingly insignificant change in a formula or a technic.

An old disease has been given a new name by an English manufacturer of laboratory apparatus. The ailment is termed "infection from parsimonicocci," and the symptoms are well known to all of us. As a remedy, the manufacturer suggests discarding the idea of saving "a few pence," followed by choosing suitable laboratory equipment to insure good service in the making of pharmaceuticals and chemicals.

AJP

After a considerable number of microchemical and microbiological determinations, certain research workers in the field of nutrition have determined the presence of thiamine, riboflavin, nicotinic acid, pantothentic acid, pyridoxine and biotin in honey. Inasmuch as these are the B vitamins, their presence in honey does not seem at all strange.

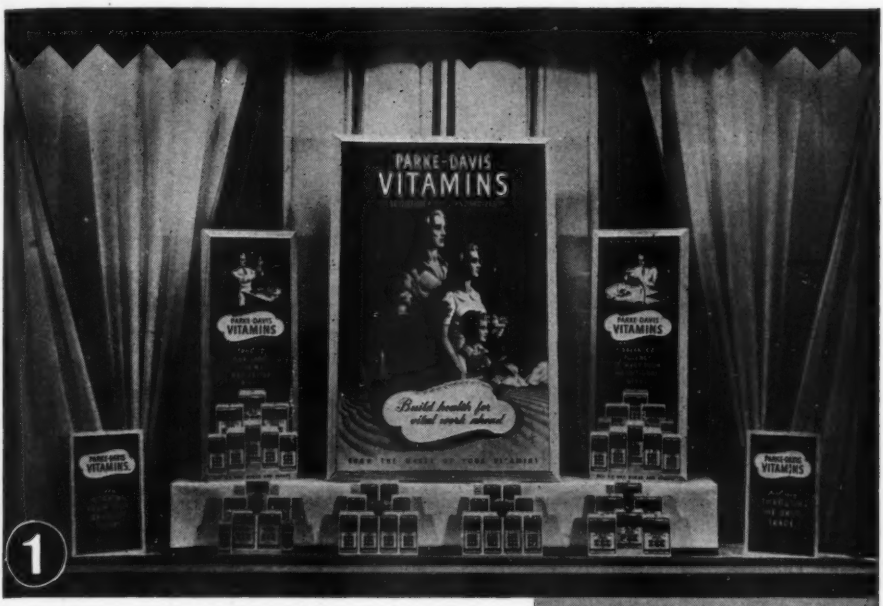
AJP

Since "Pearl Harbor" most of the rotenone-bearing plants have come to us from Pureto Rico, Costa Rica and Central American countries. The estimated need at this time is for about 20,000,000 pounds per year, to make about 90,000,000 pounds of finished insecticide. The supply, however, is insufficient to meet this great need.

In addition to being a friend of the farmer in eliminating plant pests, and a friend of the soldier in eliminating body pests, rotenone is also a friend of the doctor and some of his patients, for some good results have been obtained in the use of this substance in the treatment of scabies.

AJP

According to reliable figures, drug store sales are currently running 25% ahead of last year, and 82% over the pre-war year of 1939. This, of course, covers all departments. In our opinion the prescription department is holding its own in this increase, despite the fact that many doctors have been called into the armed services. Those doctors who have stayed behind to take care of the home front seem to be writing more prescriptions than ever.



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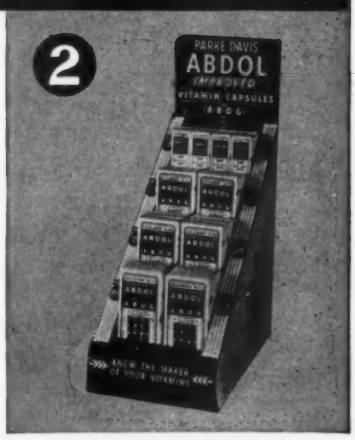

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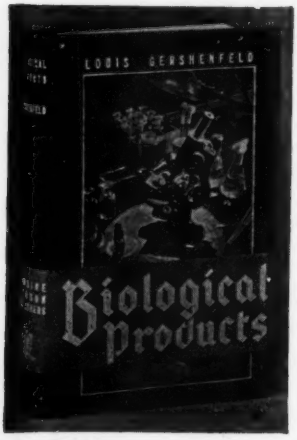

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